

Welcome to the July 2014 SMMGP Clinical Update. Summaries of the following papers are included:

- A randomized controlled trial testing the efficacy of a brief cannabis universal prevention program among adolescents in primary care.
- Under the radar: a cross- sectional study of the challenge of identifying at-risk alcohol consumption in the general practice setting.
- Pharmacotherapy for adults with alcohol use disorders in outpatient settings. A systematic review and meta-analysis.
- "Every 'Never' I Ever Said Came True": Transitions from opioid pills to heroin injecting.
- Reasons for opioid use among patients with dependence on prescription opioids: The role of chronic pain.
- The non-medical use of tramadol in the UK: findings from a large community sample.
- Factors associated with the use of cleaned needles and syringes among people who inject drugs in the UK: Who should we target to minimise the risks.
- Ledipasvir and sofosbuvir for previously treated HCV genotype 1 infection.

---

**A randomized controlled trial testing the efficacy of a brief cannabis universal prevention program among adolescents in primary care.** *Walton A, Resko S, Barry KL, et al. Addiction 2014. doi:10.1111/add.12469*

This RCT compared two different kinds of brief intervention - one delivered by a therapist (TBI) and one delivered by computer (CBI). It was based in urban primary care clinics in the USA over the period April 2007 to December 2009 and was known as Project Chill. The brief interventions from the therapists were motivational interviewing based.

The primary outcome was any cannabis use (and frequency of use was measured) and the secondary outcomes included frequency of other drug use, severity of alcohol use, and frequency of delinquency (assessed using ten items for things such as physical fighting, stealing, selling drugs).

In total they recruited 714 adolescents (aged 12 to 18 years) who had reported no lifetime use of cannabis. Compared with controls the CBI participants had significantly lower rates of any cannabis

use over 12 months - 16.8% versus 24.2%. Compared with controls the TBI participants did not differ in cannabis use or frequency - but did have less other drug use at 3 months, alcohol use at 6 months and delinquency at 3 months.

**Commentary:** One of the important numbers to pick out of the columns of figures from this study is the point prevalence of cannabis use - that gives us a feeling for the scale of the situation. That shows that just under a quarter of the controls had used cannabis by the 12 month point. So, the figure of 16.8% from the CBI group looks reasonably impressive at first glance. However, when you delve into the tables it is evident that the only time when there is any statistical difference is between CBI and controls at 12 months - when the relative risk is 0.70 (95% CI 0.48-1.00). So, the 95% CI actually touches 1.0 and it achieves statistical significance by a whisker (the confidence interval isn't reported in the abstract). The authors state this is a small but clinically meaningful effect - and we should certainly be concentrating on clinically meaningful results and not bickering over statistical significance. At no point does the TBI show a statistically significant difference between CBI and controls.

There are harms associated with cannabis. Perhaps not as great as other substances but they exist - and they certainly seem to be greater in an adolescent population like the ones studied here. It is known the effects of brief interventions dwindle with time - the authors of this study go on to suggest that adolescents could receive annual 'boosters' of CBI to help prevent cannabis use. And this is where I admit I feel some discomfort with this study - like everyone, I recognise the harms from cannabis but the underlying ethos of this study falls a little into a 'Just Say No' mentality about drugs that folk of my generation will recognise and that has heaped stigma onto ignorance onto fear that serves nobody and no generation well.

**Under the radar: a cross- sectional study of the challenge of identifying at-risk alcohol consumption in the general practice setting.** *Paul C, Lin Yoong S, Sanson-Fisher R, et al. BMC Family Practice 2014, 15:74*

This paper reported on a study based in Australia. It compared the assessments about alcohol consumption made by general practitioners (using a checklist) with self-reported use from the participants. The participants recruited also completed a modified AUDIT-C questionnaire. The study aimed to report sensitivity, specificity, positive predictive value (PPV) and negative predictive value (NPV).

There were 1,565 people where comparisons on self-report and GP completed checklist could be made. The sensitivity of the GP detection of 'at-risk alcohol consumption' was 26.5%. The specificity was 96.1%. There was an association with higher patient education and GP *non-detection* of at-risk drinking. The PPV for GPs detecting at-risk alcohol consumption was 63% and the NPV was 84%.

**Commentary:** We've covered this before and it remains an important topic for general practice: how do we identify people with alcohol problems and how far should brief interventions go? There is an underlying tension here – one usually has to look at large samples in order to see the effect of brief interventions. That population approach doesn't always square with an important philosophy of primary care that it is based around the consultation at the individual level. The population health mentality simply advocates that every time we see someone with an alcohol problem we bang on about it to them – actually, it's true, on a population level you'd probably see benefit in that particular outcome. On an individual level it's a possibility it will distort your relationship with those patients.

The paper in *BMC Family Practice* reinforces an area we've covered before. There is now good evidence that GPs are a bit rubbish at identifying people with alcohol problems when they are left to using their own nous - unless it is 'barn door' obvious. That's not necessarily because GPs are poor at identification as there are numerous possible explanations for this. The finding that those with higher education were even less likely to be picked up is an interesting one. Those who are drinking just a little more than the recommendations were also more likely to be missed and this is a group that might be most amenable to making small changes. I still think that a good underlying message from all this is that if you are at all serious about finding people who use too much alcohol then use the AUDIT questionnaire.

**Pharmacotherapy for adults with alcohol use disorders in outpatient settings. A systematic review and meta-analysis.** Jonas DE, Amick HR, Feltner C, et al. *JAMA*. 2014;311(18):1889-1900.

As one would expect of anything published in JAMA this is a nice big whopper of a systematic review. It included no less than 122 randomised controlled trials and it threw in a single cohort study to bring the total number of participants to nearly 23,000. It is an American overview and they largely stuck to FDA-approved medications. The majority of the studies were looking at acamprosate and/or naltrexone. Both of these showed that they could prevent a 'return to any drinking'. Acamprosate had a number needed to treat (NNT) of 12 and oral naltrexone had a NNT of 20. Naltrexone also had a NNT of 12 to 'prevent return to heavy drinking'. The meta-analysis of trials which compared acamprosate to naltrexone showed no significant difference between the two.

They also looked at disulfiram and only two studies were included with 492 participants. Those two studies didn't show a statistically significant reduction in drinking days but, overall, the evidence was simply not good enough to draw any conclusions. Nalmefene and topiramate both showed some benefit in some outcomes. As has been discussed before nalmefene can show some modest benefits in terms of consumption in a sub-group of drinkers who don't respond to initial contacts. Topiramate shows an association with fewer drinking days, heavy drinking days, and drinks per drinking day.

**Commentary:** The last paper about alcohol was concerned with those who are drinking slightly over the odds and who may be doing themselves harm in a more subtle fashion. The damage is obvious at the population level but harder for the individual to clock. Not so much in this group of people. They are usually to be found doing spectacular damage at the individual level. The findings from this systematic review are important – but, as expected, unfortunately far from spectacular in terms of benefit. The comment from the authors should also be borne in mind: "We found scant evidence from primary care settings."

**"Every 'Never' I Ever Said Came True": Transitions from opioid pills to heroin injecting.** Mars SG, Bourgois P, Karandinos G, et al. *Int J Drug Policy* 2014 257-266.

This paper reports on a qualitative study based in the American cities of Philadelphia and San Francisco. The authors describe this as happening during a 'pharmaceutical opioid pill epidemic'. They conducted in-depth semi-structured interviews with 22 people in Philadelphia and 19 in San Francisco.

The researchers found heroin injectors who had started with prescriptions opioids. Most users in both cities started using opioid pills with oxycodone - either in combination with paracetamol or as the short and long-acting formulations. They stood in contrast to older users who had tended to move into heroin injecting from other drugs such as cannabis, methamphetamine and cocaine. They noticed similar patterns between the two cities. People who had progressed to heroin from prescription opioids typically reported doing so for reasons of cost and the ease-of-access. Their transition usually moved from sniffing the heroin to injecting and they expressed dismay at the turn of events. Hence the title of the paper and the full quote came from a 25 year old man who had been injecting for over seven years:

*I was that type that said. "I'll never do Oxies". I was the type that said "I'll never" and every "never" I ever said came true. "I'll never shoot heroin" and you know so yeah the older guys were already doing heroin and I was like "Dude, no way, I'd rather eat a pill."*

**Commentary:** The researchers referred to themselves as ethnographers and this report is one aspect of a longer and deeper programme of research into these groups. There are many parallels in this study for anyone who uses drugs. The 'not me' approach can be recognised in many facets of people's behaviour. Why do people progress from smoking heroin to injecting? Why do people share when they say they'd 'never' do it?

The authors highlight the final irony in this study - heroin is thoroughly outlawed, subject to a 'war' and, yet, it ends up as the default option because it's the most readily available and the cheapest. The irony piles up when it becomes apparent that the healthcare market in the States created the problem and yet market forces ultimately drive these same people to heroin.

There is an enormous amount of work distilled into this report. It provides a concise overview of the opioid pill epidemic and there is much to mull over about how people transition into different levels of drug use.

### **Reasons for opioid use among patients with dependence on prescription opioids:**

**The role of chronic pain.** Weiss RD, Sharpe Potter J, Griffin ML et al. *Journal of Substance Abuse Treatment* 2014 <http://dx.doi.org/10.1016/j.jsat.2014.03.004>

This paper looked at individuals who had been enrolled in the Prescription Opioid Addiction Treatment Study (POATS) - an RCT looking at the best management for prescription opioid dependence. This particular paper reports on findings for patients in POATS who also had chronic pain.

They had 653 participants and they found that 42% of them met the criteria for chronic pain - as defined in the study as: *presence of pain beyond the usual aches and pains, excluding withdrawal pain, which had been present for at least 3 months*. This was self-reported by the participants and 92.7% of those with chronic pain had experienced it for more than a year and over half (55%) for more than four years.

Chronic pain was the most common reason given for initial use but those who met the definition of chronic pain were more likely to say this (83% vs 49%). The second most common reason was to get high (13% of chronic pain vs 39% of non-chronic pain). However, in those who had initially used for pain relief the primary reason for *current* use was given as avoiding withdrawal in 57%. A further 23% still used for pain relief and 14% to get high.

**Commentary:** Chronic pain is an important factor in the management of many patients and even more so in people with substance misuse problems - and it leads us into conditions that aren't always well-served - dental care, leg ulcer pain, and the high degree of physical trauma with poor after-care experienced in this group.

The relationship between chronic pain and prescription opioid misuse is complex, but needs unpicking to help with clinical care. If nothing else, the one thing that can be taken from this study is the definition used for chronic pain that is given above. It's not a 'validated' question as such but asking someone that question to fix in our minds whether they have chronic pain may be a useful clinical approach.

### **The non-medical use of tramadol in the UK: findings from a large community sample.**

Winstock AR, Borschmann R, Bell J. *Int J Clin Pract* doi: 10.1111/ijcp.12429

This paper reports on an anonymous online drug survey conducted in 2012. It is part of the Global Drug Survey (GDS) and 7,360 UK respondents completed it. In total there were 369 people (5%) who reported tramadol use in the past year. Just under 70% of those who had used tramadol had also used another prescription opioid in the past year. Only 2.4% reported heroin use.

A small number (3%) reported using it to control withdrawal symptoms. Nearly two-thirds had obtained their tramadol via a doctor's prescription. The other third got it from friends and they were more likely to report using it 'to get high'. Three-quarters reported using it for pain relief but more than one reason was often given – the next most common being: 'help me relax'; 'help me sleep'; 'to get high'; and 'to relieve boredom'.

**Commentary:** We've all seen problems with tramadol but it seems to be an area that has been slow to creep into the consciousness of our fellow healthcare professionals. Part of the concern around tramadol is tied into the abuse potential but this paper highlights the non-medical use in more detail. The online survey doesn't lay any claim to being representative of the general population – it was targeted at people who don't normally access services so was promoted through media such as the gay press and social media, as well as mainstream media such as the Guardian. There is a key point presented early in this paper - in just the second line of the abstract. There has, in fact, been *no* increase in people seeking treatment for prescription drug dependence in the UK. However, Winstock, Bell and Borschmann also had a short communication in the BMJ in the autumn of 2013. In that they pointed out that: "deaths due to the painkiller tramadol have doubled in the past four years to 179 last year [2012]". So far, there is no reported USA-style 'epidemic' but it remains a concern. There are still people out there with problems and they are not necessarily receiving the best treatment either.

### **Factors associated with the use of cleaned needles and syringes among people who inject drugs in the UK: Who should we target to minimise the risks?**

Hope VD, Cullen KJ, Croxford S, et al. *Int J Drug Policy* 2014. Published online ahead of print.

There has been an anonymous monitoring survey tied into substance misuse services since 1990. In 2011 the following question was added to the survey: "In the last 28 days, did you inject with a needle or syringe after it had been cleaned (e.g. with water, bleach or detergent)?" That addition forms the basis for this short report.

A total of 2,283 people participated in 2011-12. They reported that 97% had used a needle and syringe exchange program (NSP) in the previous year. Overall, sharing of needles and syringes was reported by 825 (36%) individuals. Just over half (51%) reported cleaning their needles and

syringes. Factors associated with injecting using cleaned needles and syringes included: having shared needles/syringes, spoons or filters; number of times having injected; injecting into the hands; injecting crack; reporting an injection site abscess or open wound; homelessness in the past year; and poor local NSP coverage.

**Commentary:** One of the things that appeals to me about this paper is that underpinning this report is a good deal of cold hard pragmatism. We have NSP in the UK - yet annual reports such as *Shooting Up* always show a significant number of people will re-use and share syringes. Of course the answer here is partly better NSPs and we have to keep pushing for adequate services and improved coverage, but an understanding of the sub-groups who tend to reuse their needles and syringes means we can tailor advice on effective cleaning of needles and syringes. I've no problem with that - I'll encourage people to use sterile gear but, if push comes to shove, it's better they know how to clean well than use dirty needles and syringes.

**Ledipasvir and sofosbuvir for previously treated HCV genotype 1 infection.** *Afdhal N, Rajender Reddy K, Nelson DR. N Engl J Med 2014;370:1483-93. doi:10.1056/NEJMoa1316366*

This paper is report on the phase 3 study that follows on from the phase 2 study published in the Lancet. In total 440 patients were treated and here are the sustained viral response (SVR) results in the various arms of the study:

- ¥ 94% SVR in the group that received 12 weeks of ledipasvir + sofosbuvir
- ¥ 96% SVR in the group that received 12 weeks of ledipasvir + sofosbuvir and ribavirin
- ¥ 99% SVR in the group that received 24 weeks of ledipasvir + sofosbuvir
- ¥ 99% in the group that received 24 weeks of ledipasvir + sofosbuvir and ribavirin.

No patient discontinued treatment owing to an adverse event. The most common adverse events were fatigue, headache, and nausea.

**Commentary:** It may not yet have an immediate clinical impact for primary care practitioners - it's going to take a while before these medications percolate down to the substance misuse population. And it is going to take some brave, far-sighted policy makers to ensure it does get to those who need it. Cost is going to be a major factor - but given it has been shown that an interferon/ribavirin combination is cost-effective then one would think it is very likely that ledipasvir, sofosbuvir and their ilk (and there a number of these medications making their way to market) will win the economic argument hands down. Sadly, that isn't always enough so, if nothing else, we need to know about these drugs in primary care so we can act as advocates for our patients to make darn sure they get access to them when the time comes.